

Time-controlled release of active ingredient-containing transdermal systems

The present invention relates to active-ingredient-containing transdermal systems having time-controlled release characteristics. Once applied to the skin, the transdermal systems according to the invention are able to deliver their active ingredient in two or more successive stages at different rates. As a result, unlike with prior art systems, different amounts of active ingredient can be administered to the body at different times during the application period.

Transdermal administration of medicaments by means of transdermal therapeutic systems ("patches") is state of the art medical practice today. Active ingredients for which a uniform level in the blood over time is desirable in order for the medicament to be effective are successfully administered with patches. That category includes active ingredients such as oestradiol, clonidine, fentanyl, scopolamine, flurbiprofen, diclofenac etc.. The pharmacological action of those active ingredients is maintained also when they are administered over a relatively long period, for example a number of days. Those active ingredients can be embedded in a simple manner in so-called matrix patches which are sufficiently known to the person skilled in the art; matrix patches are distinguished from other patch systems by having a purely diffusion-controlled release of active ingredient which can be described by the square root law diffusion equation (Eq. 1) formulated by Higuchi:

$$dQ_t = \frac{1}{2} k_i A t^{\frac{1}{2}}$$

(Eq. 1)

Q	quantity of medicament
k_i	liberation constant
A	surface area
t	time

For homogeneous matrices, k_i is to be substituted in accordance with Eq. 2

$$k_l = \left[Dc_s \left(\frac{2M_0}{V} - c_s \right) \right]^{-\frac{1}{2}}$$

(Eq. 2)

- D diffusion coefficient in matrix
- c_s saturation concentration of medicament in matrix
- M_0 amount of active ingredient in matrix, $t = 0$
- V matrix volume

It will be seen from that equation (1), the basic equation for all matrix-controlled forms of medication, that the delivery of active ingredient is inversely proportional to the square root of the time, that is to say, the amount released steadily decreases with time. For the resulting blood levels, this means in principle a relatively high increase immediately after application and a steady fall over the total application period. A renewed increase in blood levels can be obtained only after exchanging the patch for an unused patch.

A variant of transdermal systems that has a more complex structure is that of membrane patches (for example DE 2 135 533, Alza Corp.). They have been designed with the aim of providing a time-constant delivery of active ingredient. The release of active ingredients is described in Eq. 3 (permeation from reservoir through membranes).

$$\frac{dQ}{dt} = \frac{K_{m/r} K_{a/m} D_a q}{K_{m/r} D_m h_a + K_{a/m} D_a h_m}$$

Eq. 3

- dQ/dt liberation rate
- $K_{m/r}$ distribution coefficient membrane/reservoir
- $K_{a/m}$ distribution coefficient adhesive layer/membrane
- D_m diffusion coefficient in membrane
- D_a diffusion coefficient in adhesive layer
- q quantity of active ingredient

h_m thickness of membrane
 h_a thickness of adhesive layer

According to that equation also, the delivery of active ingredient is steady and, with long times, q becomes smaller, decreasing monotonically. In the case of - undesired - tearing of the membrane, dose dumping can occur, that is to say a release pulse in which, however, no control can be exercised over the release.

In addition to active ingredients that make possible a continuous administration over a relatively long period of time, active ingredients are also known, however, that require variable blood concentrations during the application period. The best-known examples of these, which are also available in transdermal systems, are nitroglycerine, nicotine and testosterone. When supplied continuously, nitroglycerine leads, after a few hours, to a loss in efficacy as a result of a tolerance being developed. In the early years of marketing the products, that factor was not taken into consideration sufficiently, with the result that that type of therapy with nitroglycerine met with only little acceptance among specialists. In keeping with more recent experience of therapy, today the patches are worn only for about 10 to 12 hours and are then removed to create a regeneration phase, so that, in the evening, no protection by nitrates is given. It is precisely in the early hours of the morning, however, that there is an increased incidence of attacks of Angina pectoris. With that method of administration, therefore, no protection is guaranteed unless the patients apply the patches before rising.

The patches for nitroglycerine that are on the market do not take account of that fact that the need for active ingredient varies with the time of day.

The application of nicotine-containing patches is intended to help with giving up smoking. The stimulating effect of nicotine is produced as the nicotine concentration in the blood suddenly rises when a cigarette or the like is smoked. The matrix nicotine patches available on the market, however, are able to produce only a time-constant blood level, which cannot meet the individual nicotine requirement of a smoker.

Physiologically, testosterone is made available to the body systemically in a circadian rhythm. In the early hours at around 8 o'clock, its blood concentration is at its highest,

then falls to a relative minimum towards midday to rise again slightly in the afternoon. During the night, blood levels are at their lowest. WO A 9210231 and DE 195 17 145 describe transdermal systems that, applied in the morning, lead relatively rapidly to a blood level peak which falls again towards midday. The second peak, in the afternoon, cannot be obtained with those systems. The prior art mentioned concerns reservoir systems in which the release of active ingredient begins immediately after application. The active ingredient reservoir substantially consists of alcoholic active ingredient solutions which diffuse into the skin through porous membranes. The membrane saturated with the active ingredient solution is in that case directly in contact with the skin. Such systems are difficult to manufacture and are very expensive.

The problem of the present invention is to provide an inexpensive matrix transdermal system that can be manufactured on standard machines and that meets the requirements of the body's time-dependent need for active ingredient.

In particular, the system is to enable active ingredients to be made available to the human or animal body in a variable manner.

According to the invention, therefore, a transdermal system is provided comprising:

- a) a cover layer (1),
 - b) an active-ingredient-containing polymer layer (3),
 - c) an optionally active-ingredient-containing adhesive layer (4),
- and
- d) a protective layer (5),

characterised in that the active-ingredient-containing polymer layer (3) comprises hydrophilic polymers.

The system according to the invention has the advantage that the hydrophilic polymers of the layer (3) can be etched or dissolved by moisture on the skin, as a result of which a complete breakdown of the layer (3) can occur. The active ingredients are then released and delivered to the skin of the patient in a surge.

By adjusting the loading, thickness, composition, pore size, water-permeability etc. of the layer (4) and optionally also of the layer (3), the time at which the release of active ingre-

dient or active ingredient mixture occurs can be adjusted precisely.

If the layer (4) also contains one or more active ingredients, then active ingredient is slowly delivered to the skin starting from the time of application of the system to the skin. That phase can last until the time when the surge-like active ingredient release of the layer (3) commences.

In a preferred embodiment, the polymers of the layer (3) are soluble in water.

In a preferred embodiment, the layer (3) has perforations (holes) through which the adhesive layer (4) can come into contact with the cover layer (1). Adhesion of the cover layer (1) to the polymer layer (3) is thereby increased. The diameter of the holes can be, for example, from 0.1 to 5 mm, preferably from 0.5 to 2 mm.

The transdermal system according to the invention can have an adhesive layer (2) arranged between the active-ingredient-containing polymer layer (3) and the cover layer (1), which adhesive layer (2) optionally contains active ingredient.

That system is especially advantageous when breakdown of the polymer layer (3) has occurred, since the patch continues to retain its stability.

Especially when the layer (3) is perforated and anchoring bonds pass through the perforation from layer (2) to layer (4), a considerable gain in stability is achieved.

If the layer (2) contains one or more active ingredients, then active ingredient can continue to be delivered slowly to the skin after the surge-like release by the layer (3).

The cover layer (1) comprises according to the invention materials customary *per se*, such as one or more water-vapour-impermeable materials, such as polyterephthalic acid ester or polypropylene, or one or more water-vapour-permeable materials, such as polyurethane, or one or more woven or non-woven fabrics.

In a preferred embodiment, the adhesive layer (4) and, where applicable, the adhesive layer (2) are, independently of each other, pressure-sensitive adhesive layers.

According to the invention, the active ingredient(s) in the polymer layer (3) is(are) preferably not miscible with water.

Suitable hydrophilic polymers are, for example, gelatin or cellulose esters or ethers or derivatives thereof.

The active ingredients used according to the invention can be present in the relevant layers in the form of immobilised active ingredient solution(s) or dispersion(s).

The protective layer (5) can be a re-detachable protective layer customary *per se* and can comprise a siliconised film or a silicone paper.

The transdermal system according to the invention can be so constructed that

- a) the layers (2) and (4) are free of active ingredient, or
- b) the layer (2) contains active ingredient and the layer (4) is free of active ingredient, or
- c) the layer (2) is free of active ingredient and the layer (4) contains active ingredient, or
- d) the layers (2) and (4) contain active ingredient,

the thickness of the layer (4) being from 10 to 300 μm , preferably from 30 to 100 μm , and the thickness of the layer (2) being from 1 to 300 μm , preferably from 3 to 100 μm .

Suitable active ingredients are, for example, testosterone, nitroglycerine, nicotine or mixtures thereof.

Accordingly, the transdermal system according to the invention can be used, for example, for the treatment of Angina pectoris, for nicotine withdrawal or in the case of testosterone deficiency symptoms.

A process according to the invention for the manufacture of a transdermal system according to the invention is characterised in that an adhesive layer (4) is applied to a protective layer (5), an active-ingredient-containing hydrophilic polymer layer (3) optionally having perforations is applied to the adhesive layer (4), a further adhesive layer (2) is optionally applied to the polymer layer (3) and a cover layer (1) is applied to the top layer.

The transdermal system according to the invention consists, therefore, of a multi-layer laminate, comprising a cover layer (backing, layer (1)) which can be water-vapour-impermeable, such as polyterephthalic acid ester or polypropylene, or water-vapour-permeable, such as polyurethane, or a woven or non-woven fabric. Optionally applied to that cover layer is a pressure-sensitive adhesive layer (anchoring, layer (2)); pressure-sensitive adhesives are sufficiently known to any person skilled in the art, either applied from solution or dispersion or in solvent- or dispersant-free form. That layer can contain active ingredient or be free of active ingredient; preferably, it is free of active ingredient. Applied to that adhesive layer is a layer (layer (3)) comprising or consisting of a polymer layer and an active ingredient solution or dispersion immobilised in the polymer layer. The polymer is preferably a water-soluble polymer, such as gelatin or cellulose esters or ethers. There is incorporated into the water-soluble polymer (polymer layer (3)), for example, a non-water-miscible active ingredient solution or dispersion which may form the sole active ingredient reservoir or part of the total active ingredient reservoir. Applied to the polymer layer is a further layer (layer (4)) of a pressure-sensitive adhesive which is provided for fixing the system to the skin. That layer can contain active ingredient or be free of active ingredient. It comprises or consists of, for example, the pressure-sensitive adhesives known to the person skilled in the art, which again can be applied from solution or dispersion or in a solvent- or dispersant-free form. Anchoring bonds can be passed through holes in the polymer layer (3) to join layer (2) to layer (4). Applied to the last-mentioned layer is a re-detachable protective layer (layer (5)), usually a siliconised film or a silicone paper, which is removed before the system is applied to the skin.

To explain the mode of operation of the system according to the invention, four cases can be differentiated (see Fig. 1):

i. layer (2) and layer (4) are free of active ingredient

Since the polymer active ingredient layer (layer (3)) can consist of or comprise one or more water-soluble polymer(s), the moisture on the skin has to penetrate into that layer and etch it or dissolve it in order to allow the active ingredient immobilised in it, for example in the form of emulsion droplets, to diffuse out. The breakdown of the layer (3), which occurs more or less rapidly, for example depending on the degree of loading of the layer, results in the surge-like release of a large quantity of the active ingredient which can

penetrate rapidly through the layer (4) into the skin.

Another advantage of the system according to the invention in comparison with conventional matrix systems is that, after the system has been stuck to the skin, no active ingredient delivery takes place for a time that is to be pre-set, but then a surge-like delivery of active ingredient takes place. The time can be pre-set, for example, by adjusting the thickness of the layer (4), its composition, pore size, water-permeability etc..

ii. layer (2) contains active ingredient, layer (4) is free of active ingredient

After the depletion of the polymer layer (3) described in i., further active ingredient can subsequently diffuse out of the layer (2) and begin a second, continuous release period. That construction can be used advantageously for active ingredients such as testosterone, with which, after an initially rapid release component, a slower, continuously releasing dose component is required.

iii. layer (2) is free of active ingredient, layer (4) contains active ingredient

With this construction of the system according to the invention, continuous release of active ingredient begins immediately after application from the layer (4). After a lag time determined by the thickness and composition etc. of the layer (4), the rapid release of the active ingredient component of the layer (3) described in i. begins. These systems can be used advantageously in cases where, for example, no symptoms or only mild symptoms appear at times when the body is resting, but those symptoms become markedly more severe at times when activities are begun. It is known, for example, of organic nitrates which are used in the treatment of coronary heart disease that they are most effective in the morning hours at the time when heart attacks are most frequent. In phases of relative rest by the body, on the other hand, the need for nitrate is lower. Such a system could, therefore, be applied in the evening, delivering only relatively little active ingredient during the time of rest, in order in the morning, after the appropriately set lag time, to deliver more active ingredient to the body.

iv. layer (2) and layer (4) contain active ingredient

With this construction of the transdermal system according to the invention, continuous release of the active ingredient begins after application from the layer (4), reaches its maximum value after the lag time, to be continued slowly and continuously again from the layer (2) after depletion of the polymer layer (3).

Manufacturing Process

The pressure-sensitive adhesive layer (layer (4)) is applied - with or without active ingredient dissolved or dispersed therein - to the siliconised protective layer (layer (5)). The layer can be applied from solution in organic solvents, such as *inter alia* ethyl acetate, hexane, from solution or dispersion in aqueous solvents or also in solvent-free form by means of melt-coating or by *in situ* polymerisation. The thickness of that layer can be from 10 to 300 μm , preferably from 30 to 100 μm . The active ingredient(s) contained therein can be truly dissolved or can be in microdisperse form. Combinations of a plurality of active ingredients can be used.

In a separate step, the active-ingredient-containing polymer layer (layer (3)) is manufactured by emulsifying, for example, a solution or dispersion of one or more active ingredients in a non-volatile or sparingly volatile solvent in an aqueous solution or melt of a hydrophilic polymer. The emulsion is spread onto an intermediate film. As the emulsion solidifies, liquid-filled pores, for example, form in the polymer layer. That layer is subsequently dried and produces a film in which the active ingredient solution/dispersion is present in immobilised droplets. The polymer layer can then be provided with holes having diameters of from 0.1 to 5 mm, preferably from 0.5 to 2 mm, by punching. Then, with the protective film removed, the perforated polymer layer can be laminated onto the layer (4).

In a further step, the layer (2) - with or without active ingredient dissolved or dispersed therein - is then applied to the cover layer (layer (1)). The adhesive layer can be applied from solution in organic solvents, such as *inter alia* ethyl acetate, hexane, from dispersion in aqueous solvents or also in solvent-free form by means of melt-coating or by *in situ* polymerisation. The thickness of that layer can be from 1 to 300 μm , preferably from 3 to

100 μm . The active ingredient contained therein can be truly dissolved or can be in microdisperse form. Combinations of a plurality of active ingredients can be manufactured. After curing of that layer, it is laminated onto the polymer layer (3). The adhesive layer can join with the adhesive layer (4) through the optional punched holes in the layer (3). A stable bonding-together of the system is thereby ensured even if the polymer layer (3) were to be dissolved completely during application of the system.

After punching the appropriate shape from the laminate, the transdermal system is complete.

The invention further relates to a transdermal system comprising

- a) an active-ingredient-impenetrable cover layer (11),
 - b) a hydrophilic and slightly water-soluble membrane,
 - c) an adhesive layer (14) fixed adhesively to the membrane and optionally containing active ingredient and
 - d) a detachable protective layer (15),
- the cover layer (11) and the membrane forming with each other a cavity
 - into which the active ingredient in a liquid medium has been introduced,
 - the cover layer (11) and the membrane being inert towards the active-ingredient-containing liquid medium.

The further transdermal system according to the invention can be characterised by a membrane of gelatin, agar, starch or a synthetic hydrophilic and slightly water-soluble polymer material.

The further transdermal system according to the invention can also be characterised in that the cover layer (11) is joined in a ring to the membrane or is joined directly to the adhesive layer (14).

The further transdermal system according to the invention can also be characterised in that the active ingredient is present in the form of a solution in a solvent, especially in a natural or synthetic oil, preferably turpentine oil, silicone oil or neutral oil, or in a volatile organic solvent, preferably heptane, or in a mixture thereof.

A transdermal system according to the invention can be characterised in that the cover layer (1, 11) comprises one or more water-vapour-impermeable material(s), especially polyester, preferably polyterephthalic acid ester, or polypropylene or polyethylene, or one or more water-vapour-impermeable material(s), especially polyurethane, or one or more woven or non-woven fabrics.

A transdermal system according to the invention can also be characterised in that the adhesive layer (4, 14) and/or the adhesive layer (2) are, independently of each other, pressure-sensitive adhesive layers.

A transdermal system according to the invention can also be characterised in that the adhesive layer (4, 14) and/or the adhesive layer (2) contain a net, a non-woven fabric or a woven fabric, the thread or fibre thickness thereof preferably being less than the thickness of the adhesive layer.

A transdermal system according to the invention can also be characterised in that the protective layer (5, 15) is re-detachable and is especially a siliconised plastics film or a silicone paper.

Finally, a transdermal system according to the invention can be characterised in that the active ingredient comprises testosterone, nitroglycerine or mixtures thereof.

Finally, the invention relates to the use of a transdermal system according to the invention for the treatment of Angina pectoris, for nicotine withdrawal or in the case of testosterone deficiency symptoms.

Examples

1. Testosterone-containing reservoir transdermal system

The Example describes a reservoir system in which testosterone is dissolved in a terpene-containing vegetable oil. Figure 1 shows the *in vitro* skin permeation characteristic of that system together with the Comparison Example. The Comparison Example does not contain any element that delays active ingredient permeation and

shows the permeation of testosterone purely through an adhesive membrane. The test preparations were adhesively affixed to the isolated skin of nude mice and the active ingredient diffusion was examined in known Franz cells. It becomes clear that, after a lag time of approximately 15 hours, the release of active ingredient commences almost spontaneously and exhibits a permeation rate like that of the Comparison Preparation. Further tests have shown that the length of the lag time depends on the thickness and nature of the lag time layer.

1.1. Manufacture of the adhesive layer

A commercially customary pressure-sensitive adhesive (Duro-Tak 2070) is applied by means of a suitable coating device (for example a reverse roll coater) to a siliconised carrier film (for example polyterephthalic acid ester) in such a manner that a weight per unit area of the dried adhesive of 30 g/m² results.

1.2. Manufacture of the lag time layer

10 g of gelatin, 0.2 g of polysorbate 80, 4.02 g of glycerine and 25.8 g of water are heated to approximately 80°C. Having cooled to 50°C, the gelatin solution is applied by means of a suitable coating device (for example a reverse roll coater) to a carrier film (for example polyterephthalic acid ester) in such a manner that a weight per unit area of the dried gelatin of 45 g/m² results.

1.3. Manufacture of the active ingredient solution

Testosterone is dissolved to saturation point in a terpene-containing vegetable oil (concentration: 8.6 %).

1.4. Manufacture of the transdermal system

Circular portions having a diameter of 1.5 cm are punched from the lag time layer from 1.2. The portions are pressed onto the non-covered side of the adhesive layer from 1.1. Circular portions having a diameter of 2 cm are cut from a polyterephthalic acid ester film having a thickness of 15 µm (cover film). In a suit-

able assembly machine, those film portions are placed centrally on the pieces of gelatin film and are stuck to the underlying adhesive layer while simultaneously introducing, by means of a filling needle, 0.5 ml of the active ingredient solution into the cavity formed between the gelatin film and the cover film. After withdrawing the filling needle, the filling opening is sealed and the transdermal systems having a diameter of 2 cm are punched out.

2. Testosterone-containing matrix transdermal system

The Example describes a matrix system in which an oily testosterone solution is immobilised in a hydrophilic polymer.

Figure 2 shows the *in vitro* skin permeation of a matrix system together with the Comparison Example under the conditions described in 1. A lag time of approximately 3 hours can clearly be seen.

2.1. Manufacture of the adhesive layer as described in 1.1.

2.2. Manufacture of the cover film with anchoring layer

A commercially customary pressure-sensitive adhesive (Duro-Tak 2070) is applied by means of a suitable coating device (for example a reverse roll coater) to a carrier film (for example polyterephthalic acid ester) in such a manner that a weight per unit area of the dried adhesive of 3 g/m² results.

2.3. Manufacture of the active ingredient solution as described in 1.3.

2.4. Manufacture of the active-ingredient-containing hydrophilic polymer layer

10 g of gelatin, 2.32 g of glycerine, 0.51 g of polysorbate 80 and 26 g of water are processed at approximately 60°C to form a homogenous solution. 8 g of the active ingredient solution from 2.2. are emulsified in the gelatin solution at 75°C. The emulsion is applied by means of a suitable coating device (for example a reverse roll coater) to a carrier film (for example polyterephthalic acid ester) in such a manner

that a weight per unit area of the dried gelatin with incorporated active ingredient solution of 32 g/m² results.

2.5. Manufacture of the transdermal systems

The active-ingredient-containing gelatin layer is laminated onto the non-covered side of the adhesive layer from 2.1. The adhesive layer of the cover film is in turn laminated onto the gelatin layer. The then five-layered laminate, consisting of cover film, anchoring layer, active-ingredient-containing gelatin layer, adhesive layer and siliconised polyester film, is processed in a suitable punching or cutting apparatus to form transdermal systems having a diameter of, for example, 2 cm. After removal of the siliconised polyester film, the system can be stuck onto the skin by the pressure-sensitive adhesive layer.

3. Glycerine trinitrate-containing matrix transdermal system

The Example describes a matrix system in which an oily glycerine trinitrate solution is incorporated into a gelatin layer and combined with a glycerine trinitrate-containing adhesive layer.

3.1. Manufacture of the glycerine trinitrate-containing adhesive layer

Glycerine trinitrate is dissolved in a solution of Duro-Tak 2052 in an amount such that a 10 % concentration in respect of the solids content is obtained. The solution is applied by means of a suitable coating device (for example a reverse roll coater) to a carrier film (for example siliconised polyterephthalic acid ester film) in such a manner that a weight per unit area of the dried adhesive of 50 g/m² results.

3.2. Manufacture of the glycerine trinitrate-containing gelatin layer

10 g of gelatin, 2.32 g of glycerine, 0.51 g of polysorbate 80 and 26 g of water are processed at approximately 60°C to form a homogeneous solution. 8 g of a commercially customary 10 % solution of glycerine trinitrate in neutral oil are emulsified in the gelatin solution at 75°C. The emulsion is applied by means of a suitable

3.3. Manufacture of the cover film with anchoring layer as in 2.2.

Manufacture is carried out as described in 2.5.

4. Comparison Example

The manufacture of the transdermal system is carried out analogously to Example 1, omitting the lag time layer.